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Clinical trial

Gynecological adverse effects of natalizumab administration: Case report and review of the literature

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ABSTRACT

Background: Natalizumab is administered for the treatment of relapsing-remitting multiple sclerosis (RR-MS) with high disease activity.Natalizumab therapy has been associated with adverse effects, such as progressive multifocal leukoencephalopathy, liver damage, nasopharyngitis, urinary tract infection, urticaria, cephalgia, dizziness, fatigue, nausea, fever, rigidity, anxiety and gastroenteritis.
Objective: To describe a case of a woman with RR-MS who developed recurrent vaginitis on natalizumab administration.
Methods: Case report and review of the literature.
Results: The case of a 26-year-old Caucasian woman with RR-MS, who presented with recurrent vaginitis since the initiation of treatment with natalizumab, is reported. The patient had a 4-year history of RR-MS; monotherapy with natalizumab (inj. 300 mg/month) came after one year after the initial diagnosis. Since then, she had a history of persistent gynecological infections; the repeated vaginal cultures revealed a variety of underlying pathogens. The patient underwent numerous treatments with local and systematic antibiotics as well as antifungal agents. After the initiation of probiotics and local hygiene measures, recurrences resolved and the patient remains recurrence-free at one-year follow-up.
Conclusions: Recurrent vaginitis should be taken into account as a possible adverse effect causing discomfort during long-term natalizumab treatment. Simple measures, such as probiotic administration and meticulous local hygiene, can provide adequate relief for such patients.

1. Introduction

Natalizumab is a humanized monoclonal antibody that binds to the α4 subunit of α4β1 and α4β7 integrins expressed on leukocytes and prevents the interaction with their complementary receptor VCAM-1 (vascular cell adhesion molecule-1) on endothelial cells and other ligands within the central nervous system (CNS), such as fibronectin and osteopontin. Disruption of these molecular interactions inhibits the migration of T-cells across the blood-brain barrier and reduces inflammation (Rudick and Sandrock, 2004).

Natalizumab was FDA approved in 2004 for the treatment of relapsing-remitting multiple sclerosis (RR-MS) patients with high disease activity. It is able to reduce disease activity as measured by the Expanded Disability Status Scale (EDSS) and to decrease the rate of relapses and the number of brain lesions detected by magnetic resonance Natalizumab treatment also increases circulating B cells expressing the chemokine receptor CXCR3 (Saraste et al., 2016). Studies have suggested a positive effect of natalizumab on cognition, depression, fatigue and quality of life in MS patients (Jacques et al., 2016); nevertheless, some RR-MS patients experience a clinical relapse or worsening EDSS during natalizumab therapy, probably due to the disrupted balance of T cells (Kimura et al., 2016).

Natalizumab, administered intravenously (300 mg) once per month, is commonly well tolerated. Various side effects have been reported including progressive multifocal leukoencephalopathy (PML), a rare but severe medical condition. PML is a debilitating and often fatal neurological condition resulting from infection of oligodendrocytes caused by JC-virus (JCV). Long-term treatment (over 24 months) with

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Table 1
Presentation of the main studies reporting on the urogenital infective adverse effects of natalizumab.

Study	Region and Study Period	No. of patients treated with natalizumab or combination	No. of patients with at least one AE	No. of patients that suffered from vaginitis or UTIs	No. of deaths	No. of patients that discontinued natalizumab or combination	Critical appraisal of the study
1. Polman et al. (2006)	Europe, NorthAmerica, Australia, New Zealand 2001–2006	627	596	10 Vaginitis 20 UTIs	2	52	Most common AEs were infections (79% of AEs).
2. Rudick et al. (2006)	Europe, United States 116 weeks	589 (NTZ + IFNb-1a)	584	87 UTIs	1	73	Most common AEs were infections (83% of AEs).
3. Goodman et al. (2009)	United States, Canada June 17, 2003- March 23, 2004.	55 (NTZ + GA)	50	2 UTIs	0	4	The overall rate of infection was 60% of AEs.
4. Oturai et al. (2009)	Denmark, 2006–2007	234	136	45 UTIs	0	20	81 cases of other, non-severe infections were observed, without further information about their types.
5.Outteryck et al. (2010)	France, 2007–2008	384	No precise number	No data	No data	35	AEs were a reason for discontinuation in 30 of 35 patients. There was no specification if there was or not an urogenital manifestation of NTZ.
6. Piehl et al. (2011)	Sweden, 2006–2010	1115(Clinical outcome only for 363 patients)	89	No data	0	116	Infections represented 15.6% of serious AEs and 20.5% of non-serious AEs, but there was no information about their types.
7. Putzki et al. (2010)	Germany, Switzerland 10 years	97	No data	No data	0	8	No case of opportunistic infection was mentioned. There was no specification if there was or not an urogenital manifestation of NTZ.
8. Holmen et al. (2011)	Sweden, 2006–2010	1152	129	1 UTI	7	149	Infections corresponded to 14.7% of serious AEs (pneumonia and herpes zoster) and 22.4% of non-serious AEs (19 cases).
9. Horga et al. (2011)	Spain, 12 months	112	32	No data	0	7	No further data for the nature of AEs were provided. There was no specification if there was or not an urogenital manifestation of NTZ.
10. Mancardi et al. (2011)	Italy, 2007–2010	2971	2687	No data	2	284	The most frequent AEs were infective disorders (42% of AEs); no further information about infection types is provided.
11. Fernandes et al. (2012)	Spain, 2007–2010	1364 (Data available for 1283 patients)	64	No data	No data	176	Concomitant infections were reported by 144 patients; none of these was severe. There was no specification if there was or not an urogenital manifestation of NTZ.
12. Butzkueven et al. (2014)	Europe, Australia, Canada, Argentina, 2007–2012	4821	465	18 UTIs	9	1222	The most common serious AEs were infections (1.9% of AEs).
13. Sousa et al. (2014)	Portugal, 2010–2012	393 (Data provided for 383 patients)	No precise number	No data	No data	85	The most frequent AEs were infections (3.1% of AEs) without any further information about their types.
14. O'Connor et al. (2014)	United States and other countries, 2007–2012	1094	171	9 UTIs	3	245	The most common AEs were infections (4% of patients)
15. Van Pesch et al. (2014)	Belgium, 2007–2012	563	65	1 Acute cystitis	No data	96	Severe infections were rare and isolated events (2% of AEs).
16. Prosperini et al. (2016)	Italy, 2009–2016	39	39	No data	3	27	There was no specification if there was or not an urogenital manifestation of NTZ.

AE: adverse effect; GA: glatiramer acetate; IFN: interferon; UTI: urinary track infection; NTZ: natalizumab.